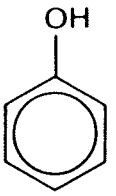
PHENOL

1. Chemical and Physical Data

1.1 Synonyms

Chem. Abstr. Services Reg. No.: 108-95-2
Chem. Abstr. Name: Phenol
IUPAC Systemic Name: Hydroxybenzene
Synonyms: Carbolic acid; monohydroxybenzene; oxybenzene; phenic acid; phenyl alcohol; phenyl hydrate; phenyl hydroxide; phenylic alcohol; phenylic acid

1.2 Structural and molecular formulae and molecular weight



C_6H_6O Mol. wt: 94.11

1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: White, crystalline solid that liquefies on absorption of water from air; acrid odour; sharp burning taste (Hawley, 1981)

(*b*) *Boiling-point*: 181.7°C at 760 mm Hg, 70.9°C at 10 mm Hg (Weast, 1985)

(*c*) *Melting-point*: 43°C (Weast, 1985)

(*d*) *Density*: 1.06 at 20°/4°C (Weast, 1985)

(*e*) *Spectroscopy data*: Infrared, ultraviolet and nuclear magnetic resonance spectral data have been reported (Sadtler Research Laboratories, 1980; Pouchert, 1981, 1983, 1985).

(*f*) *Refractive index*: 1.5408 at 41°C (Weast, 1985)

(*g*) *Solubility*: Soluble in water (82 g/l at 15°C; Considine, 1974), acetone, benzene, ethanol, diethyl ether, chloroform, glycerol, carbon disulfide and aqueous alkalies (Hawley, 1981; Windholz, 1983; Weast, 1985)

(*h*) *Volatility*: Vapour pressure: 0.357 mm Hg at 20°C (Dow Chemical Co., 1988)

(*i*) *Flash-point*: 80°C (closed cup); 85°C (open cup); mixture of air and 3-10% phenol vapour is explosive (Deichmann & Keplinger, 1981)

(*j*) *Reactivity*: Hot phenol is incompatible with aluminium, magnesium, lead, and zinc. Iron and copper catalyse discolouration. Contact with strong oxidizers and calcium hypochlorite must be avoided (Dow Chemical Co., 1988).

(*k*) *Octanol/water partition coefficient*: log P = 1.46 (Verschueren, 1983)

(*l*) *Conversion factor*: $mg/m^3 = 3.85 \times ppm$[1]

1.4 Technical products and impurities

Trade name: ENT 1814

Phenol is available in commercial grades of 82–84%, 90–92% (Considine, 1974) and 95%. Typical impurities from cumene-derived phenol include small amounts of acetol, acetone, acetophenone, *sec*-butyl alcohol, cumene, cyclohexanol, α,α-dimethylphenyl carbinol, isopropyl alcohol, mesityl oxide, 2-methylbenzofuran, α-methylstyrene and 2-phenyl-2-butene (Dow Chemical Co., 1986).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Phenol was first isolated from coal-tar in the 1830s. A relatively small but steady supply of phenol is recovered as a by-product of metallurgical coke manufacture. By-product coal-tar is fractionally distilled and the phenolic fraction extracted with aqueous alkali. Coal-tar was the only source of phenol until the First World War, when sulfonation of benzene and hydrolysis of the sulfonate led to the production of the first synthetic phenol (Considine, 1974; Thurman, 1982).

Other synthetic routes to phenol have involved the hydrolysis of chlorobenzene (diphenyl ether and *ortho*- and *para*-hydroxydiphenyl occur as by-products) and oxidation of toluene (see monograph, p. 79) to benzoic acid followed by oxydecarboxylation to phenol after purification. The chlorobenzene process and, to a lesser extent, the toluene-based process have been of major importance in phenol production in the past and are still used in some facilities (Thurman, 1982).

More than 98% of the phenol currently produced in the USA is derived from cumene (isopropylbenzene). This method is also the most commonly used method worldwide due to

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[1]Calculated from: mg/m^3 = (molecular weight/24.45) × ppm, assuming standard temperature (25°C) and pressure (760 mm Hg)

its high yield and economy. In this process, cumene is formed from benzene and propylene, then oxidized to the hydroperoxide, which is cleaved with sulfuric acid to yield phenol and acetone. Purification is achieved by distillation or ion-exchange resin separation. The total phenol yield from this process is about 93%, based on cumene and 84% based on benzene (Thurman, 1982).

Annual production of phenol by several countries is given in Table 1.

Table 1. Annual production of phenol (in thousand tonnes)[a]

Country	1980	1981	1982	1983	1984	1985	1986
Brazil	87.1	72.9	91.5	95.8	99.6	NA	NA
Czechoslovakia	43.9	42.1	45.9	45.3	43.6	42.6	46.3
Finland	1.0	2.9	29.9	NA	NA	NA	NA
India	14.1	10.3	15.0	18.0	20.0	NA	NA
Japan	215	214	211	271	272	262	260
Mexico	21.0	23.0	20.7	22.0	24.5	27.1	NA
Romania	65.7	66.0	71.7	88.4	99.6	87.9	NA
Spain	47.9	41.3	37.0	39.7	64.3	73.8	69.7
Sweden[b]	4.2	5.2	5.2	7.1	6.5	6.7	7.6
Turkey	0.1	0.1	NA	NA	NA	NA	NA
UK	NA	109.7	136.8	143.2	184.4	117.5	52.9
USA[c]	1164.8	1169.4	917.6	1196.6	1310.4	1288.7	1412.9
USSR[d]	496.0	497.0	459.0	484.0	511.0	502.0	515.0
Yugoslavia	NA	NA	NA	NA	NA	NA	2.3

[a]From Anon. (1984, 1987, 1988); US International Trade Commission (1981, 1982, 1983, 1984, 1985, 1986, 1987, 1988); NA, not available

[b]Phenol and phenol alcohols

[c]Does not include data from coke ovens and gas retorts

[d]Synthetic and crystallized from coal

(*b*) *Use*

Phenol is the basic feedstock from which a number of commercially important materials are made, including phenolic resins, bisphenol A and caprolactam (see IARC, 1987) as well as chlorophenols such as pentachlorophenol (see IARC, 1986). The products made in largest volume are the phenolic resins, derived by condensation of phenol and substituted phenols with aldehydes, particularly formaldehyde (see IARC, 1987). Phenolic resins are used as adhesives in plywood and particle board, as binders for fibreglass, mineral wool and other insulating products, for impregnating and laminating wood and plastic agents, and as moulding compounds and foundry resins (Greek, 1983; Mannsville Chemical Products Corp., 1985).

Bisphenol A is the second most important product of phenol. It is derived by reaction of phenol with acetone and is used mainly in the manufacture of epoxy and polycarbonate resins for plastic mouldings, protective coatings such as paints (see monograph on occupational exposures in paint manufacture and painting) and adhesive applications (epoxy resins), as well as in automotive, appliance, electronic, glazing and other types of applications.

Bisphenol A may also be used to produce phenoxy, polysulfone and polyester resins. Caprolactam, prepared from phenol *via* cyclohexanone as an intermediate, is used to make Nylon-6 fibres, moulding resins and plastic film (Mannsville Chemical Products Corp., 1985).

Phenol is also converted to alkyl phenols, which are used as surface-active agents, emulsifiers, antioxidants and lubricating oil additives (nonylphenols) and to make plasticizers, resins and synthetic lubricants (by conversion to adipic acid). In 1982, a US chemical company initiated the production of aniline from phenol. Another phenol derivative, 2,6-xylenol, is used to make polyphenylene oxide (Mannsville Chemical Products Corp., 1985).

Phenol was widely used in the 1800s as a wound treatment, antiseptic and local anaesthetic; the medical uses of phenol today include incorporation into lotions, salves and ointments. It is also used in the manufacture of disinfectants and antiseptics, paint and varnish removers, lacquers, paints, rubber, ink, illuminating gases, tanning dyes, perfumes, soaps and toys (National Institute for Occupational Safety and Health, 1976; Deichmann & Keplinger, 1981).

In 1986, an estimated 45% of the phenol produced in the USA was used to make phenolic resins, 25% to make bisphenol A, 15% to make caprolactam, 4% to make alkyl phenols, 4% for xylenols, and 7% for miscellaneous uses (Mannsville Chemical Products Corp., 1985).

(c) *Regulatory status and guidelines*

Occupational exposure limits for phenol in 32 countries or regions are presented in Table 2.

Table 2. Occupational exposure limits for phenol[a]

Country or region	Year	Concentration (mg/m^3)[b]	Interpretation[c]
Australia	1984	S 19	TWA
Austria	1985	S 19	TWA
Belgium	1985	S 19	TWA
Brazil	1985	15	TWA
Bulgaria	1985	S 5	TWA
Commission of the European Communities	1986	19	TWA
		95	Maximum
Chile	1985	S 15.2	TWA
China	1985	S 5	TWA
Czechoslovakia	1985	20	Average
		40	Maximum
Denmark	1988	S 19	TWA
Finland	1987	S 19	TWA
		S 38	STEL (15 min)
France	1986	S 19	TWA
Germany, Federal Republic of	1988	S 19	TWA
German Democratic Republic	1985	S 20	TWA

Table 2 (contd)

Country or region	Year	Concentration (mg/m^3)[b]	Interpretation[c]
Hungary	1985	S 5	TWA
		S 10	STEL
India	1985	S 19	TWA
		S 38	STEL
Indonesia	1985	S 19	TWA
Italy	1985	8	TWA
Japan	1988	S 19	TWA
Mexico	1985	S 19	TWA
Netherlands	1986	S 19	TWA
Norway	1981	S 19	TWA
Poland	1985	S 10	TWA
Romania	1985	S 10	Average
		S 15	Maximum
Sweden	1987	S 4	TWA
		S 8	STEL
Switzerland	1985	S 19	TWA
Taiwan	1985	S 19	TWA
UK	1987	S 19	TWA
		S 38	Stel (10 min)
USA[d]			
OSHA	1985	19	TWA
NIOSH	1983	20	TWA
		60	Ceiling (15 min)
ACGIH	1988	S 19	TWA
USSR	1986	S 0.3	Ceiling
Venezuela	1985	S 19	TWA
		S 38	Ceiling
Yugoslavia	1985	S 5	TWA

[a]From Direktoratet for Arbeidstilsynet (1981); International Labour Office (1984); Arbeidsinspectie (1986); Commission of the European Communities (1986); Institut National de Recherche et de Sécurité (1986); Cook (1987); Health and Safety Executive (1987); National Swedish Board of Occupational Safety and Health (1987); Työsuojeluhallitus (1987); American Conference of Governmental Industrial Hygienists (1988); Arbejdstilsynet (1988); Deutsche Forschungsgemeinschaft (1988)

[b]S, skin notation

[c]TWA, time-weighted average; STEL, short-term exposure limit

[d]OSHA, Occupational Safety and Health Administration; NIOSH, National Institute for Occupational Safety and Health; ACGIH, American Conference of Governmental Hygienists

2.2 Occurrence

(a) *Natural occurrence*

Phenol is a constituent of coal-tar and is formed during the natural decomposition of organic materials (Cleland & Kingsbury, 1977).

(b) *Occupational exposure*

On the basis of a US National Occupational Exposure Survey, the National Institute for Occupational Safety and Health (1983) estimated that 193 000 workers were potentially exposed to phenol in the USA in 1981–83.

Airborne phenol concentrations in area samples ranged from nondetected to 12.5 mg/m^3 in a bakelite factory in Japan (Ohtsuji & Ikeda, 1972). Exposure levels of 5–88 mg/m^3 have been reported for employees in the USSR who quenched coke with waste-water containing 0.3–0.8 g/l phenol (Petrov, 1960). Occupational exposure to 5 ppm (19 mg/m^3) in a synthetic fibre plant in Japan corresponded to a urinary phenol level of 251 mg/g creatinine (Ogata *et al.*, 1986). Air levels of phenol were correlated with urinary excretion rates in workers at five plants producing phenol, phenol resins and caprolactam in the USSR. The mean personal air and urinary phenol levels at two phenol resin plants were 0.6 mg/m^3 and 33.4 mg/l and 3.0 mg/m^3 and 34.2 mg/l, respectively; those of workers in another plant, who manufactured phenol from chlorobenzene, were 1.2 mg/m^3 and 91.3 mg/l. In a plant for the manufacture of caprolactam, the mean urinary phenol level in workers was 34.0 mg/l (air levels were not determined); and mean personal air and urinary phenol levels in workers in a plant that produced phenol from cumene were 5.8 mg/m^3 in air and 28.5 mg/l in urine (Mogilnicka & Piotrowski, 1974). Phenol levels in the air of 19 Finnish plywood plants ranged from < 0.01 to 0.5 ppm (< 0.04–1.9 mg/m^3; Kauppinen, 1986), and those at a plant in the USA that manufactured fibrous glasswool were 0.01–0.35 ppm (0.05–1.3 mg/m^3), with a mean of 0.11 ppm (Dement *et al.*, 1973).

(c) *Air*

Phenol was detected in urban air (0.55–1.01 ppb; 2–4 μg/m^3), in exhaust from cars (0.233–0.320 ppm; 0.9–1.2 mg/m^3) and in tobacco smoke (312–436 μg/cigarette) collected in Osaka, Japan (Kuwata *et al.*, 1980).

(d) *Water and sediment*

Phenols may occur in domestic and industrial waste waters, natural waters and potable water supplies. Chlorination of such waters may produce chlorophenols, giving the water an objectionable smell and taste. Processes for the removal of phenol include superchlorination, chlorine dioxide or chloramine treatment, ozonation, and activated carbon adsorption (American Public Health Association–American Waterworks Association–Water Pollution Control Federation, 1985). Phenol was found at a level of 1 μg/l in a domestic water supply in the USA (Ramanathan, 1984). It has been detected in US river water at 0.02–0.15 mg/l (Verschueren, 1983) and in industrial waste waters at average concentrations of up to 95 mg/l (US Environmental Protection Agency, 1983).

(*e*) *Soil and plants*

In studies of environmental fate, phenol has been reported to biodegrade completely in soil within two to five days (Baker & Mayfield, 1980; Verschueren, 1983). When high soil concentrations are produced by a spill, the compound may destroy the degrading bacterial population and leach through to groundwater (Delfino & Dube, 1976; Baker & Mayfield, 1980; Ehrlich *et al.*, 1982).

(*f*) *Food*

Phenol has been found to taint the taste of fish and other organisms when present at concentrations of 1.0–25 mg/l in the marine environment (Verschueren, 1983). It has been detected in smoked summer sausage (7 mg/kg) and in smoked pork belly (28.6 mg/kg; US Environmental Protection Agency, 1980).

2.3 Analysis

In the presence of other phenolic compounds, phenol is readily determined by conversion to the corresponding bromophenol by reaction with bromine. The minimal detectable amount of bromophenol by gas chromatography is about 0.01 ng (Hoshika & Muto, 1979).

Phenol present in polluted air (industrial emissions, automobile exhaust, tobacco smoke) may be collected by drawing the air through a 0.1M solution of sodium hydroxide and determined by reversed-phase high-performance liquid chromatography after derivatization with *para*-nitrobenzene diazonium tetrafluoroborate, with a detection limit of 0.05 ppb (0.2 μg/m^3) for 150 l of gas sample (Kuwata *et al.*, 1980). Phenol collected similarly can also be measured by gas chromatography with flame ionization detection. This method has been validated in the range of 10–38 mg/m^3 in 100-l samples (Eller, 1984). Air samples can be collected on a solid sorbent (e.g., resin; Cummins, 1981), and this method has been used to determine phenol in industrial waste and in natural and potable waters (American Public Health Association–American Waterworks Association–Water Pollution Control Federation, 1985).

Phenol can be determined in water samples by steam distillation followed by reaction with 4-aminoantipyrine in the presence of potassium ferricyanide to form a coloured antipyrine dye, which is determined spectrophotometrically. The sensitivity of this method is 1 μg/l (American Public Health Association–American Waterworks Association–Water Pollution Control Federation, 1985). It can also be detected at levels of approximately 0.2 μg/l by gas chromatography with flame ionization and electron capture detection following derivitization with pentafluorobenzyl bromide (US Environmental Protection Agency, 1986a).

In urine samples, phenol can be determined by acidification, diethyl ether extraction, and analysis by gas chromatography with flame-ionization detection. The limit of detection is estimated to be 0.5 μg phenol/l urine (Eller, 1985).

Environmental samples can also be analysed by gas chromatography/mass spectrometry using either packed or capillary columns. The practical quantitative limit is approximately 1 mg/kg (wet weight) for soil/sediment samples, 1–200 mg/kg for wastes and 10 μg/l for ground water samples (US Environmental Protection Agency, 1986b,c).

Colorimetric systems have been developed for detecting phenol in air (ENMET Corp., undated; Matheson Gas Products, undated; Roxan, Inc., undated; The Foxboro Co., 1983; Sensidyne, 1985; National Draeger, Inc., 1987; SKC Inc., 1988).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(*a*) *Oral administration*

Mouse: Groups of 50 male and 50 female B6C3F1 mice, five to six weeks old, were administered drinking-water containing 0, 2500 or 5000 ppm (mg/l) phenol for 103 weeks, and surviving animals were killed at weeks 104–106. Three batches of phenol were used, one with a purity of 98.47%, one with 1.36% impurities, and a homogeneous batch with one impurity. Throughout most of the study period, there was a dose-related reduction in mean body weight in both males and females and treatment-related reduction in water consumption. At weeks 104–106, 42/50 control, 45/50 low-dose and 48/50 high-dose males were still alive; at weeks 105–106, 41/50 control, 40/50 low-dose and 42/50 high-dose females survived. No treatment-related increase in the incidence of tumours was observed in mice of either sex. The incidence of uterine endometrial polyps in females was 1/50 in controls, 0/48 at the low dose and 5/48 at the high dose (National Toxicology Program, 1980).

Rat: Groups of 50 male and 50 female Fischer 344 rats, five to six weeks old, were administered drinking-water containing 0, 2500 or 5000 ppm (mg/l) phenol (purity, see above) for 103 weeks, and surviving animals were killed at weeks 104–105. After about 20 weeks of study, there was a reduction in mean body weight in both males and females which coincided with a reduction in water consumption. At weeks 104–105, 26/50 control, 22/50 low-dose and 30/50 high-dose males, and 38/50 control, 39/50 low-dose and 37/50 high-dose females were still alive. Low-dose males had increased incidences of phaeochromocytomas of the adrenal medulla (control, 13/50; low-dose, 22/50, $p = 0.046$; high-dose, 9/50), leukaemias or lymphomas (control, 18/50; low-dose 31/50, $p = 0.08$; high-dose, 22/50) and C-cell carcinomas of the thyroid (control, 0/50; low-dose, 5/49; high-dose, 1/50; National Toxicology Program, 1980).

(*b*) *Skin application*

In a wide range of studies using the two-stage mouse skin model, phenol was investigated as an initiator and a promoter with a number of polycyclic hydrocarbons. The following studies exemplify this approach.

Mouse: Three groups of 30 and one of 22 female albino mice [strain unspecified], nine weeks old, received single initiating applications of 75 μg dimethylbenz[*a*]anthracene (DMBA), given as 0.25 μl of a 0.3% solution in benzene, followed by applications of 25 μl benzene twice a week (group 1); 25 μl of a 5% solution of phenol (purified reagent grade) in

benzene twice a week (group 2); 25 μl of a 10% solution of phenol in benzene twice a week (group 3); or 25 μl of a 0.5% solution of croton oil in benzene twice a week (group 4). A further three groups of 30 mice received no DMBA treatment but applications of 25 μl of the 5% phenol solution twice a week (group 5); 25 μl of the 10% phenol solution twice a week (group 6); or 25 μl of the 0.5% croton oil solution twice a week (Group 7). Secondary treatments continued for 51 weeks, at which time the study was terminated. At week 20, the average numbers of papillomas per mouse were 6.0, 3.3 and 0.25 in groups 4, 3 and 2, respectively. Groups without DMBA pretreatment developed papillomas more slowly, and at week 36 there was a 25% incidence in groups 6 and 7 but only one mouse with papillomas in group 5. No papilloma was seen in group 1, and no skin carcinoma was reported in mice of group 1 or in those receiving 5 or 10% phenol alone (groups 5 and 6). There was a dose–related increase in the incidence of skin carcinomas in mice receiving DMBA and phenol (groups 2 and 3), with an incidence of 47% at 40 weeks in group 3 (Boutwell & Bosch, 1959).

Groups of 30 female Swiss (Millerton) mice, six weeks old, received either 75 μg DMBA in acetone (group 1); applications of a 5% purified phenol solution in acetone three times a week (group 2); applications of a 10% phenol solution in acetone three times a week (group 3); applications of a 10% phenol solution in acetone three times a week (group 4); 75 μg DMBA in acetone followed one week later by applications of the 5% phenol solution in acetone three times a week (group 5); 75 μg DMBA in acetone followed one week later by applications of the 10% phenol solution in acetone twice a week (group 6); or 75 μg DMBA in acetone followed one week later by applications of the 10% phenol solution in acetone three times a week (group 7). Treatment of groups 2–7 continued for 51 weeks, and the study was terminated at 15 months. At this time, the percentages of mice with papillomas of the skin were: group 1, 10; group 2, 0; group 3, 7; group 4, 3; group 5, 33; group 6, 87; and group 7, 80. The percentages of those with skin carcinomas were: group 1, 7; group 2, 0; group 3, 3; group 4, 0; group 5, 10; group 6, 70; and group 7, 47 (Wynder & Hoffmann, 1961).

Other, similar studies with similar results that were reviewed by the Working Group but are not summarized here are those of Salaman and Glendenning (1957), Van Duuren *et al.* (1968) and Van Duuren and Goldschmidt (1976).

(c) *Administration with known carcinogens*

Groups of female C57Bl mice, 12–14 g in weight, received 20 instillations of 1 mg benzo[*a*]pyrene in 0.1 ml triethyleneglycol twice a week by gavage simultaneously with a solution of phenol in water (1 mg in 0.1 ml). An increased incidence of forestomach tumours, including carcinomas was seen: 15/43 and 2/43 total tumours and carcinomas, respectively, in the group receiving benzo[*a*]pyrene alone *versus* 16/22 and 6/22, respectively, in the group receiving combined treatment. A lower dose of phenol (0.02 mg) did not influence the benzo[*a*]pyrene–induced carcinogenesis of the forestomach (8/23 and 1/23 total tumours and carcinomas, respectively). When administration of benzo[*a*]pyrene was followed by phenol, forestomach carcinogenesis was inhibited: 5/21 and 0/21 total tumours and carcinomas, respectively. An inhibitory effect was also observed when phenol treatment preceded benzo[*a*]pyrene: 6/24 and 0/24 total tumours and carcinomas, respectively (Yanysheva *et al.*,

1988). [The Working Group noted that the duration of the study and survival were not specified.]

Three groups of 28–40 female Swiss (Millerton) mice, six weeks old, received skin applications of approximately 5 μg of a 0.005% solution of benzo[*a*]pyrene (purified) in acetone three times a week; two of the groups also received applications of either a 5 or 10% solution of phenol in acetone alternatively with benzo[*a*]pyrene twice a week. Treatment was continued for 52 weeks, and animals were observed for 15 months. At 12 months, the percentages of mice with skin papillomas were: benzo[*a*]pyrene alone, 58; benzo[*a*]pyrene plus 5% phenol, 83; benzo[*a*]pyrene plus 10% phenol, 80. The percentages of mice with skin carcinomas were: benzo[*a*]pyrene alone, 47; benzo[*a*]pyrene plus 5% phenol, 77; benzo[*a*]pyrene plus 10% phenol, 70 (Wynder & Hoffmann, 1961).

Groups of 20 female ICR/Ha mice, six to eight weeks old, received skin applications of 0.1 ml acetone, 5 μg purified benzo[*a*]pyrene in 0.1 ml acetone or 5 μg benzo[*a*]pyrene together with 3 mg purified phenol in 0.1 ml acetone three times a week for 508, 460 or 460 days, respectively. No skin tumour was observed in the group that received acetone. In the benzo[*a*]pyrene–treated group, 8/20 papillomas and 1/20 skin carcinomas developed, compared to 3/20 papillomas and 1/20 skin carcinomas in the group treated with benzo[*a*]pyrene and phenol (Van Duuren *et al.*, 1971).

Groups of 50 female ICR/Ha mice, seven weeks old, received skin applications of 0.1 ml acetone containing 5 μg purified benzo[*a*]pyrene, 5 μg benzo[*a*]pyrene together with 3 mg purified phenol, 3 mg phenol or acetone alone three times a week for 52 weeks. At the end of the treatment period, survival was 42/50 and 39/50 in the benzo[*a*]pyrene–treated and benzo[*a*]pyrene plus phenol–treated groups, respectively. In the benzo[*a*]pyrene–treated group, 13/50 papilloma–bearing mice had a total of 14 papillomas, and 10/50 mice had squamous–cell carcinomas of the skin. In the group treated with benzo[*a*]pyrene and phenol, 7/50 papilloma–bearing mice had a total of nine papillomas and 3/50 mice had squamous–cell carcinomas. In the group treated with phenol alone, 1/50 papilloma–bearing mouse had one papilloma; no tumour was reported at 63 weeks in the group given acetone alone (Van Duuren *et al.*, 1973; Van Duuren & Goldschmidt, 1976).

3.2 Other relevant data

The toxicology of phenol has been reviewed (National Institute for Occupational Safety and Health, 1976; Bruce *et al.*, 1987).

(*a*) *Experimental systems*

(i) *Absorption, distribution, excretion and metabolism*

Phenol is absorbed through the lungs (Deichmann & Keplinger, 1981) and the alimentary tract in various species (Capel *et al.*, 1972). In addition, phenol in solution was absorbed through the clipped skin of rabbits (Freeman *et al.*, 1951; Deichmann *et al.*, 1952) and through excised clipped skin of rats at a rate directly related to the concentration of phenol up to 3% (Roberts *et al.*, 1974).

The concentration of phenol in the body of rabbits 15 min after oral administration of a 5% aqueous solution was highest in the liver, followed by the kidneys, lungs, brain and spinal

cord, and blood (Deichmann, 1944). Following oral administration of 207 mg/kg bw ^{14}C-phenol to rats, the highest concentration ratios between tissues and plasma were found in the liver followed by the kidneys, spleen, adrenal glands, thyroid gland and lungs (Liao & Oehme, 1981). Radioactivity was high in the lungs, kidneys and small intestines in autoradiograms of rats killed 2 h after intravenous injection of 0.6 mg/kg bw ^{14}C-phenol (Greenlee *et al.*, 1981).

Urinary excretion is generally rapid in various species; the percentage of radioactivity excreted within 24 h after oral administration of ^{14}C-phenol was highest in rats (95%) and lowest in squirrel monkeys (31%) among 18 species of animals tested. While absorbed phenol is excreted in the urine as conjugated phenol and a small fraction as conjugated quinol, a marked species difference is observed in the ratio of sulfate to glucuronide. Among 18 species of animals given 25 mg/kg bw ^{14}C-phenol orally, cats excreted phenyl (87%) and quinol (13%) sulfates but no glucuronide, and pigs excreted only phenyl glucuronide and no sulfate, whereas other species excreted substantial amounts of both phenyl and quinol sulfates and glucuronides (Capel *et al.*, 1972). In a similar experiment in which sheep, pigs and rats were given 25 mg/kg bw ^{14}C-phenol orally, glucuronides accounted for 49, 83 and 42% of the total urinary metabolites in the three species, respectively, and sulfates accounted for 32, 1 and 55%. Less than 7% was excreted as quinol conjugates. Only in sheep, 12% of the urinary metabolites were conjugated with phosphate (Kao *et al.*, 1979). Phenyl sulfates (80%) and quinol sulfate (20%) were detected in the urine of cats given 20 mg/kg bw ^{14}C-phenol intraperitoneally (Miller *et al.*, 1976). The ratio between sulfation and glucuronidation is dose-dependent; preferential formation of sulfate occurs at lower doses (Williams, 1959; Ramli & Wheldrake, 1981).

Phenol is metabolized in the liver and other tissues. In an experiment with an isolated gut preparation, it was shown that phenol is transported from the intestinal lumen not in the free form but conjugated. Formation and urinary excretion of phenol conjugates occur in rats even after removal of the liver and gastrointestinal tract (Powell *et al.*, 1974). In rats with cannulae in the left jugular vein and left carotid artery, about 60% of ^{14}C-phenol administered *via* the venous cannula was extracted by the lungs on the first pass following administration (Cassidy & Houston, 1980). ^{14}C-Phenol was extensively metabolized to phenyl sulfate and phenyl glucuronide in a whole rat-lung preparation (Hogg *et al.*, 1981). In comparison, a study in which phenol was administered to rats *via* the duodenal lumen and jugular and hepatic portal veins showed that intestinal and hepatic conjugation are comparable at low doses (< 1 mg/kg bw), although the capacity of the hepatic enzyme is readily saturated, whereas intestinal conjugation far exceeds the contribution of the hepatic and pulmonary enzymes after high doses (> 5 mg/kg bw; Cassidy & Houston, 1984).

^{14}C-Phenol binds irreversibly to calf thymus DNA in the presence of horseradish peroxidase and hydrogen peroxide (Subrahmanyam & O'Brien, 1985a). One of the products formed by the oxidation of phenol, *ortho,ortho'*-biphenol (but not *para,para'*-biphenol), readily binds to DNA following peroxidase-catalysed oxidation (Subrahmanyam & O'Brien, 1985b).

Phenol did not bind covalently to rat haemoglobin *in vivo* (Pereira & Chang, 1981) but was associated with plasma protein in rats *in vivo* (Liao & Oehme, 1981) and with human

serum *in vitro*, where the binding occurred predominantly (48.7%) in the albumin fraction (Judis, 1982).

(ii) *Toxic effects*

The majority of the LD_{50} values for phenol in several species fall within one order of magnitude (except for dermal application), cats being the most sensitive and pigs the most resistant species. This difference in sensitivity to the toxicity of phenol can be attributed to quantitative and qualitative differences in phenol metabolism (glucuronidation *versus* sulfatation) between species (Oehme & Davis, 1970 [abstract]; Miller *et al.*, 1973).

The oral LD_{50} for phenol in male mice was about 300 mg/kg bw (von Oettingen & Sharpless, 1946). The oral LD_{50} in different strains of rats ranged from 340–650 mg/kg bw (Deichmann & Oesper, 1940; Deichmann & Witherup, 1944; Flickinger, 1976). Dermal LD_{50}s of 1400 mg/kg bw in rabbits (Vernot *et al.*, 1977) and of 0.625 ml (660 mg)/kg bw in rats (Conning & Hayes, 1970) have been described.

On the basis of mortality during a 14–day post–exposure period, the single–dose LD_{50} for skin penetration in male albino rabbits was estimated to be 850 mg/kg bw. Phenol (500 mg) also produced necrosis after a maximal period of 24 h in the intact skin of exposed rabbits. Application of 100 mg phenol into the eyes of male albino rabbits resulted in inflamed conjunctiva and opaque corneas; 24 h after exposure, the eyes showed severe conjunctivitis, corneal opacities and corneal ulcerations, with no improvement during further observation (Flickinger, 1976). Following dermal application of phenol, rats developed severe skin lesions with oedema followed by necrosis (Conning & Hayes, 1970). Rats exposed to 900 mg/m^3 phenol–water aerosol for 8 h developed ocular and nasal irritation, loss of coordination, tremors and prostration (Flickinger, 1976).

In mice exposed to phenol vapour at concentrations of 5 ppm (19 mg/m^3) for 8 h per day on five days per week for 90 days, increased stress endurance but no significant difference in any other parameter studied (haematology, urine analysis, blood chemistry, kidney function, rate of weight gain, pathological examination) was observed. In rats exposed to phenol vapour at concentrations of 5 ppm (19 mg/m^3) for 8 h per day on five days per week for 90 days and to 100–200 mg/m^3 for 7 h per day on five days per week for 53 days over 74 days, no change in the same parameters was noted, except for a slight weight gain compared to controls. Essentially the same results were obtained in monkeys exposed to phenol vapours at concentrations of 5 ppm (19 mg/m^3) for 8 h per day on five days per week for 90 days. In guinea–pigs exposed to phenol vapours of 100–200 mg/m^3 for 7 h per day on five days per week, toxicological changes observed included weight loss, respiratory difficulties and hind–quarter paralysis. Histological examination revealed myocardial necrosis, acute lobular pneumonia and liver and kidney damage. Extensive mortality (4/12) was found in guinea–pigs after 20 exposures over 28 days. In rabbits exposed similarly, damage was in general less severe than that found in guinea–pigs after 88 days (Deichmann *et al.*, 1944; National Institute for Occupational Safety and Health, 1976).

Significant effects on the central nervous system (grasping reflex and vestibular function) in rats were observed after continuous exposure to 100 mg/m^3 phenol for 15 days; activi-

ties of serum liver enzymes were also increased, indicative of liver damage (Dalin & Kristoffersson, 1974).

(iii) *Effects on reproduction and prenatal toxicity*

As reported in an abstract, groups of 23 CD rats were exposed by oral intubation to 0, 30, 60 or 120 mg/kg bw phenol per day on days 6–15 of gestation and the fetuses examined at term for growth, viability and malformations. There was no evidence of maternal toxicity or teratogenicity, but fetal growth was retarded at the highest dose (Price *et al.*, 1986).

As reported in an abstract, groups of CD-1 mice were exposed by oral intubation to 0, 70, 140 and 280 mg/kg bw phenol per day on days 6–15 of gestation. Fetuses were examined for growth, viability and malformations. Maternal and fetal toxicity but no significant evidence of teratogenicity were observed. Greater maternal toxicity as well as cleft palates in the fetus were reported at the high dose level (Price *et al.*, 1986).

Phenol was one of a series of chemicals used in a structure–activity developmental toxicology study reported in an abstract. The chemicals were administered [route unspecified] to groups of Sprague–Dawley rats on day 11 of gestation at four dose levels between 0 and 1000 mg/kg or added to embryos of the same developmental age in whole embryo culture *in vitro*. *In vivo*, phenol induced hind-limb and tail defects. *In vitro*, phenol was the least potent of seven congeners tested; the activity, however, was increased following co-culture with primary hepatocytes (Kavlock *et al.*, 1987).

(iv) *Genetic and related effects*

Phenol was mutagenic to *Escherichia coli* B/Sd-4 at highly toxic doses only (survival level, 0.5–1.7%; Demerec *et al.*, 1951). It did not induce filamentation in the *lon*$^-$ mutant of *E. coli* (Nagel *et al.*, 1982). It was not mutagenic to *Salmonella typhimurium* TA1535, TA1537, TA1538, TA98 or TA100 in the presence or absence of an exogenous metabolic system from Aroclor-induced rat and hamster livers (Cotruvo *et al.*, 1977; Epler *et al.*, 1979; Florin *et al.*, 1980; Gilbert *et al.*, 1980; Kinoshita *et al.*, 1981; Thompson & Melampy, 1981; Pool & Lin, 1982; Haworth *et al.*, 1983; Kazmer *et al.*, 1983; Ludewig & Glatt, 1986 [abstract]). It was mutagenic to *S. typhimurium* TA98 only in the presence of an exogenous metabolic system when the assay was performed using a modified medium (ZLM) instead of the standard Vogel–Bonner medium (Gocke *et al.*, 1981).

Phenol weakly induced mitotic segregation in *Aspergillus nidulans* (Crebelli *et al.*, 1987). It induced C-mitosis in the root tips of *Allium cepa* but only rarely induced chromosomal fragmentation (Levan & Tjio, 1948). It induced chromosomal aberrations in maize and wheat [details not given] (Chebotar *et al.*, 1975).

Phenol did not increase the frequency of recessive lethal mutations in *Drosophila melanogaster* (Sturtevant, 1952). Feeding or injection of phenol did not induce sex-linked recessive lethal mutations in meiotic or postmeiotic germ-cell stages of adult male *Drosophila* (Gocke *et al.*, 1981; Woodruff *et al.*, 1985).

Phenol did not induce DNA single-strand breaks in mouse lymphoma L5178YS cells (Pellack-Walker & Blumer, 1986). It was reported in an abstract that phenol induced DNA strand breaks in mouse lymphoma cells, as measured by the alkaline unwinding technique followed by elution through hydroxylapatite (Garberg & Bolcsfoldi, 1985). It was reported in

a further abstract that phenol did not induce strand breaks, as measured by the alkaline elution technique, in rat germ-cell DNA after either acute or subchronic treatment (Skare & Schrotel, 1984).

Phenol induced mutations at the *hprt* locus of Chinese hamster V79 cells in the absence of an exogenous metabolic system from the livers of phenobarbital-induced mice (Paschin & Bahitova, 1982).

Phenol was reported to inhibit DNA synthesis in HeLa cells (Dobashi, 1974; Painter & Howard, 1982) and to inhibit repair of radiation-induced chromosomal breaks in human leucocytes (Morimoto *et al.*, 1976). However, it only slightly inhibited DNA repair synthesis and DNA replication synthesis in WI-38 human diploid fibroblasts (Poirier *et al.*, 1975). Phenol induced sister chromatid exchange in human lymphocytes (Morimoto & Wolff, 1980a,b; Erexson *et al.*, 1985a,b); the number of sister chromatid exchanges was further increased by the presence of an exogenous metabolic system from rat livers (Morimoto *et al.*, 1983). In another study, phenol was reported to be incapable of inducing sister chromatid exchange in human lymphocytes (Jansson *et al.*, 1986).

Administration of phenol either intraperitoneally (two doses of 188 mg/kg bw; Gocke *et al.*, 1981) or orally (250 mg/kg bw; Gad-el Karim *et al.*, 1986) to female and male NMRI or male CD-1 mice did not induce micronuclei in bone marrow. However, phenol induced micronuclei in the bone marrow of pregnant CD/1 mice after a single administration of 265 mg/kg bw by gastric intubation; micronuclei were not seen in the liver of fetuses (Ciranni *et al.*, 1988). As reported in abstract, phenol induced micronuclei in male and female mice at doses of 150 and 200 mg/kg bw (Sofuni *et al.*, 1986). It was reported in another abstract that phenol induced chromosomal aberrations in bone marrow of mice *in vivo* [details not given] (Lowe *et al.*, 1987). Phenol did not inhibit intercellular communication (as measured by metabolic cooperation) in Chinese hamster V79 cells (Chen *et al.*, 1984; Malcolm *et al.*, 1985).

(*b*) *Humans*

(i) *Absorption, distribution, excretion and metabolism*

Studies in human volunteers have shown that 70–80% of inhaled phenol vapour is retained (Piotrowski, 1971) and that phenol is absorbed almost quantitatively through the alimentary tract (Capel *et al.*, 1972). Phenol in lotion, ointment (Rogers *et al.*, 1978) and vapour form (Piotrowski, 1971) can penetrate the skin. When absorbed, almost all of the dose is excreted in the urine within one day (Piotrowski, 1971; Capel *et al.*, 1972). In male volunteers given 0.01 mg/kg bw ^{14}C-phenol orally, 90% of the dose was excreted within 24 h, mainly as phenyl sulfate (77% of 24-h excretion) and phenyl glucuronide (16%), together with very small amounts of quinol sulfate and glucuronide (Capel *et al.*, 1972).

Exposure-dependent increases in the concentration of phenol in urine have been observed among factory workers occupationally exposed to phenol vapour (Ohtsuji & Ikeda, 1972; Knapik *et al.*, 1980; Gspan *et al.*, 1984). The increase was attributable entirely to conjugated phenol, and no significant change in the concentration of free phenol was observed, regardless of the intensity of exposure to phenol vapour (up to 13 mg/m^3 in workroom air; Ohtsuji & Ikeda, 1972).

(ii) *Toxic effects*

Phenol poisoning occurs by skin absorption, vapour inhalation or ingestion. Phenol has a marked corrosive effect on all tissues and, on contact with skin, causes whitening of the exposed area followed by severe chemical burns; long after cessation of contact, progressive areas of depigmentation may develop (Pardoe *et al.*, 1976).

Application of a bandage containing 2% phenol to the umbilicus of a newborn baby resulted in death after 11 h. Another newborn baby treated with 30% phenol:60% camphor for a skin ulcer experienced circulatory failure, cerebral intoxication and methaemoglobinaemia but recovered after a blood transfusion (Hinkel & Kintzel, 1968). An accidental spill in industry resulting in cutaneous absorption also caused death (Griffiths, 1973).

After an acute percutaneous intoxication of a chemical worker with phenol, local effects on the skin were seen in conjunction with several effects due to systemic intoxication, including massive intravascular haemolysis, tachycardia, respiratory depression, and renal and liver damage. The latter was concluded from the increased activities of liver enzymes in the serum (Schaper, 1981). Ingestion of 10–56 ml phenol caused severe irritation in the gastrointestinal tract, cardiovascular collapse, respiratory depression and seizures (Bennett *et al.*, 1950; Stajduhar-Caric, 1968).

As reported in a review, exposure by inhalation to low concentrations of phenol (0.004 ppm; 0.015 mg/m^3) six times for 5 min produced increased sensitivity to light in three volunteers adapted to the dark. Exposures to 0.006 ppm (0.02 mg/m^3) phenol for 15 sec resulted in the formation of conditioned electrocortical reflexes in four volunteers (Bruce *et al.*, 1987).

'Phenol marasmus', described as an occupational hazard resulting from chronic exposure to phenol, involves anorexia, weight loss, headache, vertigo, salivation and dark urine (Merliss, 1972).

Repeated oral exposure for several weeks (estimated intake, 10–240 mg/day) due to contamination of groundwater after an accidental spill of phenol resulted in mouth sores (burning of the mouth), diarrhoea and dark urine. Examination six months after the exposure revealed no residual effect (Baker *et al.*, 1978).

(iii) *Effects on fertility and on pregnancy outcome*

No data were available to the Working Group.

(iv) *Genetic and related effects*

As reported in an abstract, increased frequencies of chromosomal aberrations were found in peripheral lymphocytes of 50 workers occupationally exposed to formaldehyde, styrene and phenol, as compared to 25 controls (Mierauskienė & Lekevičius, 1985).

3.3 Epidemiological studies of carcinogenicity in humans

Wilcosky *et al.* (1984) performed a case–control study in a cohort of rubber workers (see the monograph on some petroleum solvents, p. 69). Exposure to phenol was associated with an increased risk for stomach cancer (relative risk, 1.4; six cases). [The Working Group noted that the number of cases in each category is small and multiple exposures were evaluated independently of other exposures.]

Kauppinen *et al.* (1986) conducted a case–control study of 57 male cases of 'respiratory' tumours, defined as cancers originating in organs in direct contact with chemical agents, such as the tongue, mouth, pharynx, nose, sinuses, larynx, epiglottis, trachea and lung; approximately 90% were of the lung and trachea. Three control subjects for each case (171 men) were selected from the same cohort of 3805 men who had started working in one of 19 Finnish plywood, particle–board, sawmill and formaldehyde glue plants in 1944–65, had worked for at least one year and had been followed up from 1957 to 1981. Exposure histories were assessed for each control until the month of diagnosis of his matched case. A job–exposure matrix was used to determine exposures, in which the emphasis was on wood dust exposure and chlorophenols; other exposures were determined qualitatively (yes/no) and as a function of exposure time. Smoking histories were obtained. The relative risks for exposure to phenol, adjusted for smoking, were 4.0 (12 cases; $p < 0.05$) and 2.9 with a requirement of ten years' latency (seven cases, $p > 0.05$). The relative risks for 'phenol in wood dust' were also increased but diminished after the requirement of ten years of latency time. Relative risks for exposure to phenol did not increase with duration of exposure, and the authors noted confounding by exposure to pesticides.

4. Summary of Data Reported and Evaluation

4.1 Exposures

Phenol is a basic feedstock for the production of phenolic resins, bisphenol A, caprolactam, chlorophenols and several alkylphenols and xylenols. Phenol is also used in disinfectants and antiseptics. Occupational exposure to phenol has been reported during its production and use, as well as in the use of phenolic resins in the wood products industry. It has also been detected in automotive exhaust and tobacco smoke.

4.2 Experimental carcinogenicity data

Phenol was tested for carcinogenicity by oral administration in drinking–water in one strain of mice and one strain of rats. No treatment–related increase in the incidence of tumours was observed in mice or in female rats. In male rats, an increase in the incidence of leukaemia was observed at the lower dose but not at the higher dose. Phenol was tested extensively in the two–stage mouse skin model and showed promoting activity.

4.3 Human carcinogenicity data

In one case–control study of workers in various wood industries, an increased risk was seen for tumours of the mouth and respiratory tract in association with exposure to phenol; however, the number of cases was small and confounding exposures were inadequately controlled.

4.4 Other relevant data

In humans, phenol poisoning can occur after skin absorption, inhalation of vapours or ingestion. Acute local effects are severe tissue irritation and necrosis. At high doses, the

most prominent systemic effect is central nervous system depression. Phenol causes irritation, dermatitis, central nervous system effects and liver and kidney toxicity in experimental animals.

Phenol induced micronuclei in female mice and sister chromatid exchange in cultured human cells. It did not inhibit intercellular communication in cultured animal cells. It induced mutation but not DNA damage in cultured animal cells. It did not induce recessive lethal mutation in *Drosophila*. It had a weak effect in inducing mitotic segregation in *Aspergillus nidulans*. Phenol did not induce mutation in bacteria. (See Appendix 1.)

4.5 Evaluation[1]

There is *inadequate evidence* for the carcinogenicity of phenol in humans.
There is *inadequate evidence* for the carcinogenicity of phenol in experimental animals.

Overall evaluation

Phenol *is not classifiable as to its carcinogenicity to humans (Group 3).*

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[1]For definitions of the italicized terms, see Preamble, pp. 27–30.

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